UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

25 January 2007

MEMORANDUM

Subject:	Name of Pesticide Product:	DUPONT CYMOXANIL TECHNICAL
	EPA Reg. No. /File Symbol:	352-591
	DP Barcode:	D328899
	Decision No.:	367053
	PC Code:	129106 [Cymoxanil: 98.7%]
From:	Byron T. Backus, Ph.D., Toxicologist Technical Review Branch Registration Division (7505P)	
To:	Lisa Jones/Mary Waller, RM 21 Fungicide Branch Registration Division (7505P)	
Registrant:	E. I. DU PONT DE NEMOURS AND CO., INC.	

Byron T. Backus 1-25-2007

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
129106 Cymoxanil	98.7%
Inert Ingredient(s):	1.3%
Total:	100.0%

ACTION REQUESTED: The Risk Manager requests:

"Please review the attached cymoxanil dermal sensitization studies (MRIDs 467498-12 and -13)..."

BACKGROUND:

The material received for review consists of two dermal sensitization studies (MRIDs 46749812 and 46749813) conducted on technical Cymoxanil. It is noted that these studies were not conducted on DuPont's product (EPA Reg. No. 352-591), but on two different lots from another manufacturer, Oxon Italia. Since one of these studies (MRID 46749813) gave positive results, these studies were apparently submitted under the requirements of FIFRA 6(a)(2).

COMMENTS AND RECOMMENDATIONS:

1. One (MRID 46749813) of the studies showed a strong dermal sensitization response, the other (MRID 46749812) was negative.

2. In the study with a strong dermal sensitization response, Alembicol D (a product of coconut oil) was the solvent or suspending agent for the induction injection and topical applications, as well as the challenge. In the study without a positive response, the vehicles used were 0.5% carboxymethylcellulose (CMC) for the induction injection, and paraffin oil for the topical induction application; paraffin oil was also used as the vehicle. There is a possibility then that the Cymoxanil was in some way potentiated by the Alembicol D, but this would have to be established with additional testing.

3. The positive study was completed on May 25, 1994, while the negative study was completed on May 6, 2003. The positive study utilized a technical that was 97.6% pure, while the negative study used material that was 99.4% pure. No information was provided as to what impurities were present in either of these formulations (although the 2.4% vs. 0.6% between the positive and negative batches is suggestive), and how these compare with DuPont's registered product. In addition, no information is provided as to whether or not these two batches of Cymoxanil were manufactured using the same process, and how these compare to the manufacturing process for DuPont's product.

4. The previously submitted dermal sensitization studies on Cymoxanil (as well as Cymoxanil-containing formulations) that the Agency has received and reviewed have been consistently negative.

5. Given the above considerations and the uncertainties in interpreting the conflicting results from these two dermal sensitization studies, TRB recommends no regulatory action at this time. If the registrant wishes to consider additional testing, it is possible that a Mouse Local Lymph Node Assay conducted on EPA Reg. No. 352-591 would provide a more conclusive answer.

Reviewer: Byron T. Backus, Ph.D. **Date:** January 25, 2006
Risk Manager: 21

STUDY TYPE: Dermal Sensitization – albino Guinea Pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: Cymoxanil; 1-(2-Cyano-2-methoxyiminoacetyl)-3-ethylurea, Lot No. 793, purity: 97.6%; described as a whitish powder which was stored at room temperature in the dark.

CITATION: Allan, S.A. (1994). Cymoxanil Skin Sensitisation in the Guinea-Pig. Huntingdon Research Centre, Ltd., Cambridgeshire, England. Huntingdon Project: OXN-44-940205-SS. Study completed on May 25, 1994. MRID 46749813. 23 p. Unpublished.

SPONSOR: OXON Italia, SpA, Italy

SUBMITTER: DU PONT DE NEMOURS AND CO., INC.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46749813) with Cymoxanil, Lot No. 793, a white powder with a purity of 97.6%, a group of 15 (10 test, 5 control) young (6-7 week) adult female Dunkin/Hartley albino guinea pigs (weight: 380-646 g; source: D. Hall, Newchurch, Staffordshire, England) were tested using the Magnusson-Kligman maximization protocol. Based on preliminary irritation testing, a 1% w/v suspension in Alembicol D was used for the induction intradermal injection, and a 40% w/v suspension in Alembicol D was used for the topical induction application. Initially, 3 pairs of [0.1 mL?] injections were made into a 2 x 4 cm area on the back of each test animal immediately behind the ears. For the test guinea pigs, the paired injections consisted of 1) Freund's Complete Adjuvant (FCA); 2) Cymoxanil, 1% w/v in Alembicol D; and 3) Cymoxanil, 1% w/v in a 50:50 mixture of FCA and Alembicol D. Controls were similarly injected, but without the Cymoxanil.

Six days after the injections the application site was shaved and the site was pre-treated by gentle rubbing with 0.2 mL of 10% w/w sodium lauryl sulphate in petrolatum. Twenty-four hours later a 20 x 40 mm piece of filter paper saturated with approximately 0.4 mL Cymoxanil, 40% w/v in Alembicol D, was placed on the site and covered with plastic adhesive tape, which was in turn secured by an elastic adhesive bandage. Exposure was for 48 hours. Controls were similarly treated, but without the Cymoxanil.

Two weeks after the topical induction application, all (test & control) animals were challenged at two sites. At one site a 20 x 20 mm patch of filter paper saturated with about 0.2 mL Cymoxanil, 40% w/v in Alembicol D, was used, and at the other site a similarly-sized filter paper saturated with about 0.2 mL Cymoxanil 20% w/v in Alembicol D was used, with 24-hour exposure.

In this study, all ten test animals showed a positive response at the 40% w/v site, and 9/10 showed a positive response at 24 hours at the 20% w/v site. Most continued to show positive responses at the 48 and 72-hour readings. None of the controls showed a response (all scores zero).

The report includes summaries of positive control studies using formalin as test material (two challenge sites, 5% and 1% concentrations). The last positive control study (10/10 induced guinea pigs with positive results) prior to this report was finished on 13 February 1993 (the experimental phase of the study on Cymoxanil was conducted between 24 February and 30 March 1994).

Although the most recent positive control study was conducted more than 6 months prior to the Cymoxanil study, the unequivocal results in the latter indicate that Cymoxanil technical tested positive as a dermal sensitizer. This study is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the guinea pig.

COMPLIANCE: Signed and dated GLP (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2a) statements are provided.

PROCEDURE

A. Induction – Based on preliminary irritation testing, a 1% w/v suspension in Alembicol D was used for the induction intradermal injection, and a 40% w/v suspension in Alembicol D was used for the induction topical application. Initially, 3 pairs of [0.1 mL?] injections were made into a 2 x 4 cm area on the back of each of 10 test animals (female Dunkin-Hartley albino guinea pigs) immediately behind the ears. The paired injections consisted of 1) Freund's Complete Adjuvant (FCA); 2) Cymoxanil, 1% w/v in Alembicol D; and 3) Cymoxanil, 1% w/v in a 50:50 mixture of FCA and Alembicol D.

Six days after the injections the application site was shaved and the site was pre-treated by gentle rubbing with 0.2 mL of 10% w/w sodium lauryl sulphate in petrolatum. Twenty-four hours later a 20 x 40 mm piece of filter paper saturated with approximately 0.4 mL Cymoxanil, 40% w/v in Alembicol D, was placed on the site and covered with plastic adhesive tape, which was in turn secured by an elastic adhesive bandage. Exposure was for 48 hours.

B. Challenge – Two weeks after the topical induction application, each of the test animals was challenged at two sites. At one site a 20 x 20 mm patch of filter paper saturated with about 0.2 mL Cymoxanil, 40% w/v in Alembicol D, was used, and at the other site a similarly-sized filter paper saturated with about 0.2 mL Cymoxanil 20% w/v in Alembicol D was used, with 24-hour exposure.

C. Naïve Controls – A group of 5 female guinea pigs served as controls. These animals received similar intradermal injections and topical applications, but without the Cymoxanil. Their first exposure to Cymoxanil came when they were treated (like the previously exposed guinea pigs) at challenge.

RESULTS and DISCUSSION:

A. Reactions and Durations – All ten of the previously induced guinea pigs showed a positive response at 24 hours at the 40% w/v site, and 9/10 showed a positive response at the 20% w/v

site, and most continued to show positive responses at 48 and 72 hours. None of the negative controls showed a positive response.

B. Positive Control - The report includes summaries of positive control studies using formalin as test material (two challenge sites, 5% and 1% concentrations). The last positive control study (10/10 induced guinea pigs with positive results) prior to this report was finished on 13 February 1993 (the experimental phase of the study on Cymoxanil was conducted between 24 February and 30 March 1994).

C. Reviewer's Conclusion – Although the most recent positive control study was conducted more than 6 months prior to the Cymoxanil study, the unequivocal results in the latter indicate that Cymoxanil technical tested positive as a dermal sensitizer. This study is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the guinea pig.

Reviewer: Byron T. Backus, Ph.D. **Date:** January 25, 2006
Risk Manager: 21

STUDY TYPE: Dermal Sensitization – albino Guinea Pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: Technical Cymoxanil; 1-(2-Cyano-2-methoxyiminoacetyl)-3-ethylurea, Batch 29800123; Ref. number U017/03), purity (analytically determined): 99.4%; described as a white to light pink crystalline powder which was stored at room temperature, sheltered from light.

CITATION: Freulon, I. (2003). Technical Cymoxanil (batch 29800123 – Ref. number: U017/03): Skin Sensitisation in the Guinea-Pig (Magnusson-Kligman Maximisation). Centre de Recherches Biologiques, 18800 Baugy, France. Study completed on May 6, 2003. MRID 46749812. 58 p. Unpublished.

SPONSOR: OXON Italia, SpA, Italy

SUBMITTER: DU PONT DE NEMOURS AND CO., INC.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46749812) with technical Cymoxanil, Lot No. 793, Batch 29800123, a white to light pink crystalline powder with an analytical purity of 99.4%, a group of 15 (10 test, 5 control) adult male Dunkin/Hartley albino guinea pigs (weights: 481.3-511.3 g; source: HARLAN, Horst, the Netherlands), were tested using the Magnusson-Kligman maximization protocol. Based on preliminary irritation testing, a 1% w/v solution in 0.5% carboxymethylcellulose (CMC) was used for the intradermal induction injection, and a 25% w/v suspension in paraffin oil was used for the topical induction and challenge applications.

Initially, 3 pairs of 0.1 mL injections were made on the back (intrascapular region) of each guinea pig. For the test animals, the paired injections consisted of 1) Freund's Complete Adjuvant (FCA) diluted to 50% with sterile isotonic sodium chloride solution; 2) Technical Cymoxanil, 1% w/v in 0.5% carboxymethylcellulose; and 3) a 1:1 v/v mixture of FCA and 0.5% aqueous carboxymethylcellulose with 1% w/v Cymoxanil. Controls were similarly injected, but without the Cymoxanil.

Seven days after the injections 0.5 mL of a suspension of 10% sodium lauryl sulphate in mineral oil was applied topically to the application site. One day later the ten test animals received a topical application of 0.5 mL of a 25% w/v suspension of technical Cymoxanil in paraffin oil on an 8 cm^2 piece of absorbent gauze. Exposure was for 48 hours. Controls were similarly treated with 0.5 mL paraffin oil.

Following this 48-hour exposure, the guinea pigs were rested for 11 days. All animals (induced as well as control guinea pigs) were then challenged with exposure for 24 hours to 0.5 mL of a 25% w/v suspension of technical Cymoxanil in paraffin oil on a 4 cm^2 piece of absorbent gauze at a previously unused dermal site.

In this study, none of the 10 test or 5 negative control animals showed a positive response following challenge.

The report includes (p. 58) a table of individual results from a positive control study utilizing DNCB (1% for the intradermal induction injection treatment; 1% DNCB for the topical induction and challenge treatments). All 5 of the induced guinea pigs showed a positive response at both 24 and 48 hours (although there is no indication that there were negative controls in this assay). This positive control assay (study no. 20030099 RT was conducted in the period from February 25 to March 21, 2003 (the experimental phase of the study on Cymoxanil was also conducted between February 25 and March 21, 2003).

This study, with its negative findings, is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the guinea pig.

COMPLIANCE: Signed and dated GLP (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2a) statements are provided.

PROCEDURE

A. Induction – Based on preliminary irritation testing, a 1% w/v suspension in 0.5% carboxymethylcellulose (CMC) was used for the intradermal induction injection, and a 25% w/v suspension in paraffin oil was used for the topical induction and challenge applications.

Initially, 3 pairs of 0.1 mL injections were made on the back (intrascapular region) of each guinea pig. For the test animals, the paired injections consisted of 1) Freund's Complete Adjuvant (FCA) diluted to 50% with sterile isotonic sodium chloride solution; 2) Technical Cymoxanil, 1% w/v in 0.5% carboxymethylcellulose; and 3) a 1:1 v/v mixture of FCA and 0.5% aqueous carboxymethylcellulose with 1% w/v Cymoxanil.

Seven days after the injections 0.5 mL of a suspension of 10% sodium lauryl sulphate in mineral oil was applied topically to the application site. One day later the ten test animals received a topical application of 0.5 mL of a 25% w/v suspension of technical Cymoxanil in paraffin oil on an 8 cm^2 piece of absorbent gauze. Exposure was for 48 hours.

B. Challenge – Following the 48-hour topical induction, the guinea pigs were rested for 11 days. The test animals were then challenged using a 24-hour exposure to 0.5 mL of a 25% w/v suspension of technical Cymoxanil in paraffin oil, applied on an 8 cm^2 piece of absorbent gauze at a previously unused dermal site.

C. Naïve Controls – A group of 5 male guinea pigs served as controls. These animals received similar induction treatments as the test animals, but without the Cymoxanil. Their first exposure to Cymoxanil came when they were treated (like the previously induced test animals) at challenge.

RESULTS and DISCUSSION:

A. Reactions and Durations – In this study, none of the 10 test or 5 negative control animals showed a positive response following challenge.

B. Positive Control - The report includes (p. 58) a table of individual results from a positive control study utilizing DNCB (1% for the intradermal induction injection treatment; 1% DNCB for the topical induction and challenge treatments). All 5 of the induced guinea pigs showed a positive response at both 24 and 48 hours (although there is no indication that there were negative controls in this assay). This positive control assay (study no. 20030099 RT was conducted in the period from February 25 to March 21, 2003 (the experimental phase of the study on Cymoxanil was also conducted between February 25 and March 21, 2003).

C. Reviewer's Conclusion – Under the conditions of this study, technical Cymoxanil was not a dermal sensitizer. This study is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the guinea pig.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D328899
2. **PC CODE:** 129106 (Cymoxanil: 98.7%)
3. **CURRENT DATE:** 25 January 2007
4. **TEST MATERIALS:** Technical Cymoxanil; 1-(2-Cyano-2-methoxyiminoacetyl)-3-ethylurea, Lot No. 793, purity: 97.6%; described as a whitish powder which was stored at room temperature in the dark (MRID 46749813).

Technical Cymoxanil; 1-(2-Cyano-2-methoxyiminoacetyl)-3-ethylurea, Batch 29800123; Ref. number U017/03), purity (analytically determined): 99.4%; described as a white to light pink crystalline powder which was stored at room temperature, sheltered from light (MRID 46749812).

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Dermal sensitization / guinea pig / Huntingdon Research Centre, England / Huntingdon Project: OXN-44-940205-SS / 25-MAY-1994	46749813	Female Dunkin-Hartley albino guinea pigs used; Magnusson-Kligman Maximization Protocol: 1% w/v Cymoxanil suspension in Alembicol D was used for intradermal induction injection, and 40% w/v suspension in Alembicol D was used for the topical induction and one of the two (the other was 20% w/v) challenge applications. All 10 previously induced animals showed a strong sensitization response.	Positive Sensitizer	A
Dermal sensitization / guinea pig / Centre de Recherches, France / CERB Project 20030095 ST / 6-MAY-2003	467349812	Male Hartley albino guinea pigs used; Magnusson-Kligman Maximization Protocol: 1% w/v Cymoxanil solution in 0.5% carboxymethylcellulose used for induction intradermal injection, and a 25% w/v suspension of Cymoxanil in paraffin oil was used for the topical induction and challenge applications. None of the previously induced or 5 negative control guinea pigs showed a sensitization response. Concurrent control (DNCB) was acceptable.	Negative	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived